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Decreased centrality of subcortical regions during the transition to adolescence: A functional connectivity study

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A B S T R A C T

Investigations of brain maturation processes are a key step to understand the cognitive and emotional changes of adolescence. Although structural imaging findings have delineated clear brain developmental trajectories for typically developing individuals, less is known about the functional changes of this sensitive development period. Developmental changes, such as abstract thought, complex reasoning, and emotional and inhibitory control, have been associated with more prominent cortical control. The aim of this study is to assess brain networks connectivity changes in a large sample of 7- to 15-year-old subjects, testing the hypothesis that cortical regions will present an increasing relevance in commanding the global network. Functional magnetic resonance imaging (fMRI) data were collected in a sample of 447 typically developing children from a Brazilian community sample who were submitted to a resting state acquisition protocol. The fMRI data were used to build a functional weighted graph from which eigenvector centrality (EVC) was extracted. For each brain region (a node of the graph), the age-dependent effect on EVC was statistically tested and the developmental trajectories were estimated using polynomial functions.

Our findings show that angular gyrus become more central during this maturation period, while the caudate; cerebellar tonsils, pyramis, thalamus; fusiform, parahippocampal and inferior semilunar lobe become less central. In conclusion, we report a novel finding of an increasing centrality of the angular gyrus during the transition to adolescence, with a decreasing centrality of many subcortical and cerebellar regions.

Introduction

The transition from childhood to adolescence involves major changes in cognitive and emotional functions (Paus, 2005; Rubia, 2014). Evidence supports that such changes are a result of important refinements in complex neural dynamics and may ultimately reflect the organization of the human brain (Fair et al., 2009; Kelly et al., 2009; Stevens et al., 2009; Dosenbach et al., 2010; Blakemore, 2012).

The brain can be conceptualized as a set of partially segregated networks emerging from a complex relationship between a variety of nerve cells organized into circuits and functional areas (Power et al., 2010). Neurodevelopmental studies investigating the trajectories of these complex networks may shed light on the hierarchical structure of such circuitries during development. These types of studies are especially important in transitional periods, such as adolescence, as they can advance our understanding of this window of vulnerability for disruptions in typical development and increased incidence of mental disorders (Kim-Cohen et al., 2003; Ernst et al., 2006; Insel, 2009; Salum et al., 2010).

Several brain structural changes occur during this period. Although some regions exhibit linear changes in cortical thickness and volume,

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others appear to follow a maturational course, with an initial childhood increase until approximately 7–10 years of age and a subsequent adolescent decline (Giedd, 2004; Gogtay et al., 2004; Shaw et al., 2008). This decline in thickness during adolescence is followed by a period of slower decline, stabilizing in adulthood (Shaw et al., 2008; Sowell et al., 2003).

Intrinsic functional connectivity (Biswal et al., 1995; Buckner et al., 2013) based on fMRI is sensitive to coupling dynamics and has the ability to broadly survey the whole brain, providing information about relationships between networks (Buckner et al., 2013). The first studies investigating the development of brain networks (Fair et al., 2007, 2008, 2009; Dosenbach et al., 2010) focused on the organizing principles of such development and found evidence of functional segregation of nearby functional areas across time, which occur through the weakening of short-range functional connections. These studies also detected the integration of distant regions in a functional network, which occur by strengthening long-range functional connections. Subsequent studies more specifically investigated the meaning of such connections and addressed important questions, such as communication between cortical and subcortical areas that are thought to undergo dramatic changes over time, especially in adolescence (Paus, 2005; Lebel et al., 2008; Supekar et al., 2009; Blakemore, 2012; Rubia, 2014). Studies have suggested that children have stronger subcortical-cortical and weaker cortico-cortical connectivity compared to young adults (Supekar et al., 2009). Some research (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012) has shown that earlier developmental studies could have been influenced by head movement artifacts. These may bias functional connectivity by decreasing long-distance correlations (of BOLD signal) and increasing short-distance correlations. Interestingly, many initial findings were replicated in a recent study, even after adjusting for movement (Satterthwaite et al., 2013a).

A method that is increasingly being used to investigate the relevance of brain network nodes comes from a branch of mathematics called graph theory. In graph theory, a network is a collection of items (nodes) that possesses pairwise relationships (edges). Graphs represent the collection of nodes and edges. There are a variety of methods to characterize how important or central a node is to the network, and each seems to capture independent aspects of brain networks (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; Sporns, 2011; Zuo et al., 2012). Investigating a variety of measures of centrality can reveal how brain regions communicate and characterize network properties that support inter-regional interactions (Hwang et al., 2013).

Nevertheless, few studies have investigated developmental changes of these brain networks in periods of high incidence (or onset) of many psychiatric disorders. Moreover, studies so far have included samples with potential selection bias, such as those composed of voluntary research subjects or specific populations (Uher and Rutter, 2012). Therefore, it is unclear if such developmental effects can be easily translated to population samples. In addition, most studies relied on relatively small sample sizes (fewer than one hundred) and concentrate solely on American and European populations (Satterthwaite et al., 2013b), which are limited on miscegenation (genetic admixture) and environmental factors (e.g., education and violence). Lastly, all available studies have been performed in high-income countries, and to the best of our knowledge, there are no neuroimaging development studies in low- and middle-income countries based on large samples.

This study examines a unique large community sample from a developing country (Brazil) with high levels of genetic admixture. It is important to highlight that, due to environmental factors (e.g., poverty, violence, poor education and medical assistance, etc.), children living in developing countries are more vulnerable to mental disorders and represent the majority of such cases worldwide (Kieling et al., 2009). Thus, the investigation of children and adolescents under these environmental and genetic factors is crucial to enhance the comprehension of the typical neurodevelopment.

Here, we performed a whole-brain graph analysis aiming to identify brain regions with age-effects on eigenvector centrality (EVC) measure. Given previous empirical evidence demonstrating a process of cortical maturation (Fair et al., 2007, 2008, 2009; Supekar et al., 2009; Shaw et al., 2008; Satterthwaite et al., 2013a), the existence of developmental changes in global network properties (Hwang et al., 2013) and the presence of hub regions in adults (Power et al., 2013), we hypothesize that age-related changes occur in the central regions of brain networks, with an increase in cortical integrative regions.

Materials and methods

Participants

The participants of this study are a subsample ($N = 447$, healthy children) of the *High Risk Cohort Study for Psychiatric Disorders in Childhood* (HRC, $N = 2512$ children). For a detailed description of this cohort, see Salum et al. (2013, in press). The current investigation was based on healthy children from two different Brazilian centers in the cities of São Paulo and Porto Alegre. The study was approved by the local ethics committee (University of Sao Paulo, IORG0004884, 1138/08) and required written consent from all parents and verbal assent from all children. From the total cohort of 2512 subjects, 1004 children were invited to participate in the MRI scanning. Seven hundred forty-one subjects (and the parent/guardian) accepted the invitation and were scanned. From these, 447 children were healthy and presented typical development (229 males; mean age $\pm$ standard deviation: 9.51 $\pm$ 1.92, from 7 to 15 years old; 248 scanned at São Paulo and 199 at Porto Alegre). None of the volunteers fulfilled any criteria for psychiatric diagnoses (further details on Salum et al., 2013, in press) based on the Development and Well-Being Assessment (DAWBA, Goodman et al., 2000) interview (answered by the parents, guardian or caregiver). On the day of neuroimaging data acquisition, parents/caregiver also filled the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001). The estimation of intelligence quotient (IQ) was carried out using the vocabulary and block design subtests of the Weschler Intelligence Scale for Children, using the method proposed by Tellegen and Briggs (1967). The socioeconomic status was assessed using the Brazilian rating scale (ABIMEP) and categorized into very low/low (E and D classes), medium (C and B classes) and comfortable (A class) groups. Fig. 1 depicts the summary of demographical information.

In São Paulo, the scans were performed at the Institute of Radiology (INRAD) of the Hospital das Clínicas and in Porto Alegre at Santa Casa Foundation. The volunteers and parents did not receive any financial compensation for participating in this study, according to the laws established by the Brazilian Federal Ethics Committee for experiments involving humans.

On the day of the examinations, recreational techniques were used as a desensitization method to improve adherence and decrease movement during MRI scans. In addition, a simulation of the MRI acquisition procedure using a child's fabric play tunnel. Before the start of the acquisition of the resting-state fMRI data, the technician asked the child to look at the black dot painted on the magnet and not to sleep. Another verbal contact was performed after the acquisition to ensure that the child was awake.

Image acquisition and resting state protocol

The image acquisition was carried out in two 1.5-T MRI scanners (models Signa HDX and HD from G.E., United States of America) using the same parameters and protocols. Functional MRI acquisition consisted of 180 EPI volumes (TR = 2000 ms, TE = 30 ms, slice thickness = 4 mm, gap = 0.5 mm, flip angle = 80°, matrix size = 80×80, NEX = 1, slices = 26, total acquisition time = 6 min). The fMRI images were obtained during a resting state protocol with the eyes open and a fixation point (a small black dot painted inside the